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(54) 7-Substituted camptothecin derivatives and process for their preparation.

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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 88, no. 16, 20th August 1966, COLUMBUS, OHIO (US), pages 3888-90; M.E. WALL et al.: "Plant Antitumor Agents. I. The Isolation and Structure of Camptothecin, a Novel Alkaloidal Leukemia and Tumor Inhibitor from Camptotheca Acuminata"

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Description

This invention relates to new camptothecin derivatives possessing anti-tumor activity (including carcinostatic activity) and to processes for their preparation. More particularly, this invention relates to new camptothecin derivatives having an aldehydr group or a functionally modified aldehyde group in the 7-position thereof and possessing anti-tumor activity with a low level of toxicity, as well as processes for their preparation.

Camptothecin is a cytotoxic alkaloid isolated from the leaves and bark of Camptotheca accuminata (Nyssaceae), a plant native to China, which has a pentacyclic structure consisting of a characteristic fused 5-ring system of quinoline (rings A and B), pyrroline (ring C), α-pyridone (ring D) and a six-membered lactone (ring E) and is distinguished by displaying a strong inhibitory activity toward biosynthesis of nucleic acids. In addition, camptothecin is a unique anti-tumor substance characterised by its rapid and reversible action and its lack of any cross-tolerance with the existing anti-tumor agents and by exhibiting a strong anti-tumor activity against experimentally transplanted carcinoma such as leukemia L-1210 in mice or Walker 256 tumor in rats. Although camptothecin is still regarded as one of the most potent substances possessing anti-tumor activity, the use of this compound itself for clinical treatments is significantly limited because of its high toxicity.

Accordingly, a number of attempts have been made to reduce the toxicity of camptothecin, while maintaining its anti-tumor activity, by converting camptothecin chemically into its derivatives. The chemical modifications so far reported are mainly in relation to rings D and/or E of camptothecin, but the results of such modifications revealed only failure in maintaining the expected anti-tumor activity and a poor improvement in toxicity [J. Med. Chem., *19* (1976), 675]. From the chemotherapeutic point of view, therefore, it is of importance that the chemical modifications of camptothetin should be restricted to the rings A, B and C without effecting any change in the rings D and E which are considered to be one of the essential structural elements for the expression of the above mentioned characteristic biological activities.

Except for a method of inserting a functional group at the 12-position of camptothecin reported in 1976 which comprises a series of troublesome conversion and purification operations starting with nitration at the 12-position [P. Pei-chuang et al., Hau Hsueh Pao *33*, (1975); Chem. Abstr. *84* (1976) 115629p], however, no success was reported until 1979 in connection with the introduction of a functional group in camptothecin in a moiety involving the rings A, B and C. This is probably attributable to the reasons that camptothecin itself is only sparingly soluble in various organic solvents and that since camptothecin possesses heterocyclic rings in its molecule it is resistant to the so-called electrophilic reactions conventionally carried out on aromatic rings.

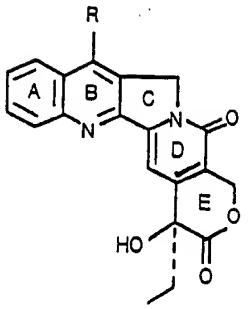
We have previously found together with co-workers a process for introducing a hydroxymethyl group into the 7-position of camptothecin efficiency in a single step and we have prepared a number of new camptothecin derivatives possessing anti-tumor activity with slight toxicity from 7-hydroxymethyl-camptothecin obtained according to the above process (Japanese Laid-open Patent Applns. Nos. Sho. 56-12391, 56-12392, 56-12393 and 56-12394; USSN 166,953; DOS 30 26 172). However, the types of camptothecin derivatives prepared according to these processes are still limited.

For further research on the relationship between the substituents in camptothecin derivatives and anti-tumor activity and/or toxicity, therefore, there is still a great demand in this field for developing further new classes of camptothecin derivatives possessing a low level of toxicity whilst maintaining the inherent anti-tumor activity by chemically modifying 7-hydroxymethylcamptothecin in a single step without destroying the structure of the rings D and E in the camptothecin molecule.

With a view of preparing new 7-substituted camptothecin derivatives possessing the inherent anti-tumor activity of camptothecin with an extremely reduced toxicity, the present inventors have made further researches for chemically modifying the hydroxymethyl group existing in the 7-position of camptothecin, taking careful attention to the chemical modifications lest any destruction should occur in the structure of the rings D and E. We have found surprisingly that the 7-hydroxymethyl, 7-alkoxymethyl or 7-dialkoxy-methyl groups in camptothecin can be converted into a 7-formyl(aldehyde) group in a single step without attacking the rings D and E and that the 7-formyl group in the resultant camptothecin derivative can be used for the preparation of various functionally converted aldehyde derivatives according to the methods known per se.

We have now developed new 7-substituted camptothecin derivatives which possess a good anti-tumor activity and good absorbability in the living body with very low toxicity, as well as processes for the preparation of such new 7-substituted camptothecin derivatives and a new process for converting a 7-hydroxymethyl group in camptothecin into a 7-formyl group or its acetal group.

In accordance with the present invention, there are provided new 7-substituted camptothecin derivatives of the general formula:



(I)

where R represents —CHO, —CH_2OR'', —$CH(OR')_2$, or —CH=N—X where R' is a lower alkyl group having from 1 to 6 carbon atoms or a phenylalkyl group having from 1 to 3 carbon atoms in the alkylene moiety thereof, R'' is a phenylalkyl group having from 1 to 3 carbon atoms in the alkylene moiety thereof, and X is a hydroxyl group or —NR^1R^2 where R^1 and R^2 are the same or different and each represent a hydrogen atom or a lower alkyl group having from 1 to 6 carbon atoms, or when R^1 is hydrogen, R^2 may be a lower alkyl group having from 1 to 6 carbon atoms, a substituted or unsubstituted aryl group, a carbamoyl group, an acyl group, an aminoalkyl group or an amidino group, or when R^1 is a lower alkyl group, R^2 may be an aminoalkyl group, or R^1 and R^2 may be combined together with the nitrogen atom to which they attached to form a heterocyclic group, and the acid-addition and quaternary salts thereof.

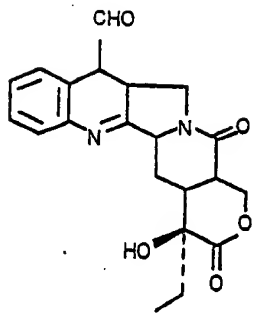
When R', R^1 and/or R^2 represent a lower alkyl group having from 1 to 6 carbon atoms, this group may be linear or branched. Typical examples of the lower alkyl group include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, n-hexyl and 2-methylpentyl groups. In view of the availability of alkanols as alkylating reagents, preferred lower alkyl groups are methyl, ethyl, n-propyl, isopropyl and n-butyl groups. The alkylene group of the phenylalkyl group has 1 to 3 carbon atoms and may be linear or branched. Preferred phenylalkyl groups are benzyl and phenethyl groups. A preferred aryl group is a phenyl group which may be substituted by one or more nitro groups, lower alkyl groups or halogen atoms. The amino-alkyl group preferably has 1 to 6 carbon atoms and may be linear or branched. The acyl group is preferably a residue of an aliphatic carboxylic acids having from 1 to 6 carbon atoms or benzoic acid which may be substituted by a lower alkyl group, alkoxy group, nitro group and/or a halogen atom. When R^1 and R^2 each represent a lower alkyl group, these groups may be combined together to form an alkylene group and may form a 5-membered or 6-membered heterocyclic group together with the nitrogen atom to which they are attached. The alkylene group may be interrupted by one or two hetero atoms such as nitrogen, oxgen and sulphur atoms.

The new 7-substituted camptothecin derivatives of this invention possess anti-tumor activity with slight toxicity. Illustrative of the typical 7-substituted camptothecin derivatives of the present invention are 7-dibutoxymethylcamptothecin, camptothecin-7-aldehyde, camptothecin-7-aldehyde oxime, camptothecin-7-aldehyde hydrazone, camptothecin-7-aldehyde methylhydrazone, camptothecin-7-aldehyde phenyl-hydrazone, camptothecin-7-aldehyde, 2,4-dinitrophenylhydrazone, camptothecin-7-aldehyde thiosemicarbazone, camptothecin-7-aldehyde semicarbazone, camptothecin-7-aldehyde hydrazone with 1-amino-4-methylpiperazine, camptothecin-7-aldehyde hydrazone with pyridinium aceto-hydrazide, camptothecin-7-aldehyde hydrazone with dimethylaminoacetohydrazide, camptothecin-7-aldehyde hydrazone with 1-amino-oxazoline.

The 7-substituted camptothecin derivatives of the general formula (I) wherein R represents the group —CH=N—X where X is especially an amino group —NR^1R^2 form acid-addition and quaternary salts thereof with an acid such as hydrochloric acid or an alkyl halide such as methyl or ethyl bromide. These quaternary salts including acid-addition salts are of course included in the scope of the present invention.

In accordance with the present invention, there is also provided a process for the preparation of the new 7-substituted camptothecin derivatives of the general formula (I).

In one embodiment of the process, camptothecin-7-aldehyde of the formula:



(I')

is prepared in a single step by treating 7-hydroxymethylcamptothecin with a cationic reagent.

The cationic reagents which may be used in this reaction include a variety of mineral (or inorganic) acids and organic acids, Lewis acids, organic acid halides and halogenating agents. Examples of the mineral or inorganic acids are sulfuric acid, hydrochloric acid, hydrobromic acid, perchloric acid and hydroiodic acid. Such acid is preferably used as a 20—50% aqueous solution to which 7-hydroxymethylcamptothecin is added. A solution of the 7-hydroxymethylcamptothecin thus formed is then boiled under reflux for a given period of time. Examples of the organic acids are carboxylic acids such as acetic acid, propionic acid, chloroacetic acid, benzoic acid and trifluoroacetic acid, and sulfonic acids such as p-toluenesulfonic acid, methanesulfonic acid and ethanesulfonic acid. These cationic agents are preferably used in a solvent, for example, a polar solvent such as water, dimethylformamide, alcohols, dimethylsulfoxide, dioxane or tetrahydrofuran. When acetic acid or a similar organic acid is used as the cationic reagent, such an organic acid also functions as a solvent. Examples of Lewis acids which may be used as another type of cationic reagent include boron trifluoride etherate, aluminium chloride, ferric chloride and stannic chloride. In this case, the Lewis acid is used in a 5—10 molar amount in an aprotic solvent such as nitrobenzene, dioxane, tetrachloroethane or diglyme, and the reaction is preferably conducted at 90—100°C. Examples of organic acid halides which may be used as still another type of cationic reagent include p-toluenesulfonyl chloride and phenylacetyl chloride. In this case, the organic acid chloride is used preferably in a 5—10 molar amount in a polar solvent such as dimethylformamide, dimethylsulfoxide, dioxane or pyridine, and the reaction is preferably carried out at 90—100°C. Halogenating agents, for example, reagents usually employed for chlorination such as phosphorus oxychloride, thionyl chloride, phosphorus trichloride or triphenylphosphine-carbon tetrachloride can also be used as the cationic reagent. In this case, such a halogenating agent is preferably used in a 5—10 molar amount in a solvent such as pyridine or dioxane, and the reaction is carried out preferably, at about 100°C.

After completion of the reaction, the solvent used is removed by evaporation under reduced pressure and the residue is subjected to column chromatography on silica gel in a usual manner. Chloroform alone or a solvent mixture containing chloroform as a predominant ingredient, is used for this chromatographic purification treatment.

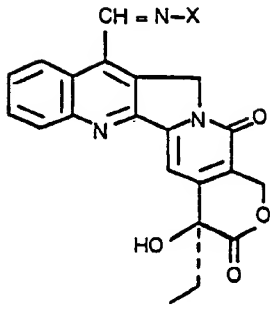
According to this embodiment, the hydroxymethyl group of 7-hydroxymethylcamptothecin can be converted into a formyl group in a single step without using an oxidizing agent. Such as oxidizing method is indeed novel and has not been known hitherto even in the treatment of ordinary primary alcohols or heterocyclic compounds such as hydroxymethylquinoline.

7-hydroxymethylcamptothecin used as the starting material in this embodiment can be readily prepared in one step from the naturally occurring (+)-camptothecin or the corresponding (−)- and dl-camptothecins synthetically obtained, according to the process disclosed in Japanese Laid-open Patent Appln. No. 56-12391 (USSN 166,953; DOS 30 26 172).

Camptothecin-7-aldehyde (7-formylcamptothecin) thus prepared is effective as an anti-tumor agent with reduced toxicity but is also useful as an intermediate product for the preparation of various new 7-substituted camptothecin derivatives utilizable as anti-tumor agents which are lower in toxicity than camptothecin itself.

According to one route for further modifying the camptothecin-7-aldehyde, an ordinary acetalization treatment can be applied to this product to obtain a 7-dialkoxymethylcamptothecin and carried out by heating camptothecin-7-aldehyde in an excess amount of R'OH in the presence of an acid in a usual manner.

According to another route for further modifying the camptothecin-7-aldehyde, an active amino compound known as a nitrogen-containing carbonyl reagent can be used is a usual manner for chemically modifying the carbonyl function of camptothecin-7-aldehyde. More precisely, various new 7-substituted camptothecin derivatives of the general formula:



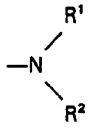
(I'')

where X is as previously defined as well as quaternary salts thereof, are prepared by reacting camptothecin-7-aldehyde or an acetal thereof with an active amino compound of the general formula:

$$H_2N—X \qquad (II)$$

wherein X is as previously defined, in a manner known per se and optionally treating the resultant product with a quaternizing agent.

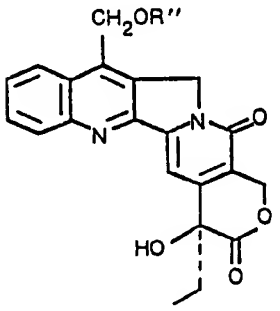
Examples of the active amino compound of the general formula (II) include hydroxylamine; hydrazine derivatives such as hydrazine itself, methylhydrazine, ethylhydrazine, phenylhydrazine, p-bitrophenylhydrazine, 2,4-dinitrophenylhydrazine and p-toluene-sulfonylhydrazine, N-aminoguanidine, 1-amino-4-methylpiperazine; Girard reagents such as N,N-dimethylglycinhydrazide hydrochloride, trimethylammonium acetohydrazide chloride, pyridinium acetohydrazide chloride and N-aminohydantoin; isonicotic acid hyrazide; semicarbazide derivatives such as semi-carbazide, phenylsemicarbazide and thiosemicarbazide; semioxazoline. Camptothecin-7-aldehyde is reacted according to a method known per se with the active amino compound preferably in an appropriate solvent such as methanol, ethanol, pyridine, acetic acid or a mixture of ethanol and pyridine at a temperature ranging from room temperature 80°C. If the active-amino compound is in the form of a salt such as the hydrochloride or sulfate, the reaction will be conducted in pyridine or together with a base such as sodium acetate, triethylamine or pyridine in an amount equivalent to the acid contained in the salt so that the active amino compound may be reacted in the free form with camptothecin-7-aldehyde. In the reaction of camptothecin-7-aldehyde with hydroxylamine, camptothecin-7-aldoxime, camptothecin-7-aldoxime in E-form and Z-form are obtained almost in a ratio of 1:1. Camptothecin-7-aldehyde hydrazones obtained by the reaction with 1-amino-4-methylpiperazine or a Girard reagent can be dissolved in water by quaternizing their



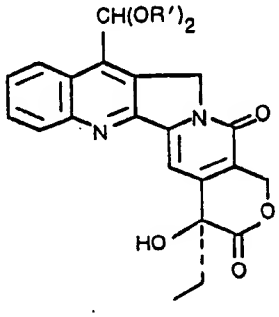
moiety with a quaternizing agent such as hydrochloric acid or a similar inorganic acid or an alkyl halide.

A variety of new 7-substituted camptothecin derivatives of the general formula (I'') are also useful as anti-tumor agents with low toxicity.

In another embodiment of the process of this invention 7-phenylalkoxymethyl- and 7-dialkoxymethylcamptothecins of the general formulae:



(I'''—A) and



(I'''—B)

wherein R' and R'' ar as defin d above are prepared in a single step by treating 7-hydroxymethylcamptothecin with an acid in the presenc of a lower alkanol or phenylalkanol of the general formula:

$$R'—OH \text{ or } R''—OH \qquad (III)$$

wherein R' and R'' have the same meaning given above.

The lower alkanols of the general formula (III) include, for example, methanol, ethanol, propanol, isopropanol, n-butanol, isobutanol, tert-butanol, n-amul alcohol, isoamyl alcohol, tertamylalcohol, n-hexamol and 2-ethylbutanol. Illustrative of the phenylalkanols are, for example, benzyl alcohol, phenethyl alcohol and phenylpropanol. Examples of the acids utilizable for this reaction are mineral acids such as sulfuric acid, hydrochloric acid, hydrobromic acid and perchloric acid; Lewis acids such as boron trifluoride, aluminium chloride, ferric chloride and stannic chloride; strong organic carboxylic acids such as trifluoroacetic acid and trichloroacetic acid; and organic sulfonic acids such as benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid and ethanesulfonic acid.

The above reaction is preferably carried out maintaining 7-hydroxymethylcamptothecin in a lower alcohol or phenylalkanol of the general formula (III) as a solvent in the presence of the above mentioned acid at a temperature of from room temperature to reflux temperature. When the acid is used in a catalytic amount or several molar equivalent amounts, a 7-dialkoxymethylcamptothecin is obtained exclusively or preferentially. On the other hand, when the acid is used in a large excess amount, e.g. in a 150—250 molar equivalent amount, together with a phenylalkanol of formula R''—OH, a 7-phenylalkoxymethylcamptothecin is obtained exclusively or preferentially. In the event that both a 7-dialkoxymethylcamptothecin and a 7-alkoxymethylcamptothecin are formed concurrently, both products can be separated and purified by subjecting the reaction product to column chromatography on silica gel or high speed fluid chromatography. The 7-dialkoxymethylcamptothecin thus obtained has a structure corresponding to an acetal of camptothecin-7-aldehyde which, as described previously with respect to the further modification of camptothecin-7-aldehyde, is obtainable in a high yield by heating the 7-aldehyde in an excess amount of a lower alkanol in the presence of an acid under the conditions usually employed for acetalization.

On the other hand, the 7-dialkoxymethylcamptothecin can be converted theoretically into camptothecin-7-aldehyde according to methods known per se, for example, hydrolysis under acidic conditions.

According to this embodiment, 7-hydroxymethylcamptothecin can be converted with a cheap reagent into 7-phenylalkoxymethylcamptothecins and 7-dialkoxymethylcamptothecins in a single step. It is indeed surprising that 7-hydroxymethylcamptothecin can be converted into a 7-dialkoxymethylcamptothecin which corresponds to an acetal of camptothecin-7-aldehyde without using any oxidizing agent. Such method is indeed novel, as in the firstly mentioned embodiment, and has not been known hitherto even in the treatment of ordinary primary alcohols, or heterocyclic compound such as hydroxymethylquinoline.

The present invention is of particular significance in developing a number of new camptothecin derivatives useful as anti-tumor agents possessing anti-tumor activity with slight toxicity and as intermediate products for preparing other useful products as well as processes for preparing these new derivatives in a simple operation.

The present invention will now be illustrated in more detail by way of Examples. In these Examples, the temperature is shown in centigrade (°C) and the parts and percentages are by weight unless otherwise indicated.

Example 1

7-Hydroxymethylcamptothecin (200 mg, 0.529 m-mol) was suspended in water (20 ml) and conc. sulfuric acid (6 ml) in small portions was added thereto to make the whole to a solution. The solution was boiled under reflux for 30.5 hours. The reaction mixture was, after allowed to stand for cooling, diluted with ice water (500 ml) and extracted with $CHCl_3$ (300 ml × 3). A solid substance insoluble in both of the aqueous phase and the $CHCl_3$ phase was collected by filtration and dried (recovery of 7-hydroxymethylcamptothecin). The $CHCl_3$ layers were combined, dried over $MgSO_4$, filtered and concentrated until dryness under reduced pressure. The residue was purified by way of column chromatography ($CHCl_3$) on silica gel whereupon 39 mg (yield: 29.7%) of camptothecin-7-aldehyde was obtained. 7-Hydroxymethylcamptothecin recovered was 68 mg in total. Analytical data of the camptothecin-7-aldehyde were as shown below.

Yellow prismatic crystals

M.P. 256—260° (dec.) (from benzene),

IR ν_{max}^{KBr} cm^{-1}: 3350, 3080, 2960, 2925, 2860, 1750 (lactone), 1690 (CHO), 1655 (lactam), 1600, 1460, 1225, 1155, 765.

NMR ($CDCl_3$ δ: 1.18 (3H, t, J=7.5 Hz), 1.93 (2H, q, J=7.5 Hz), 5.31 (1H, d, J=16 Hz, C_{17}—H), 5.63 (2H, s, C_5—H), 5.80 (1H, d, 16 Hz, C_{17}—H), 7.68 (1H, s, C_{14}—H), 7.90 (2H, m), 8.38 (1H, m), 8.80 (1H, m, C_9—H), 11.20 (1H, s, C*H*O).

MS: m/e 376[M^+] ($C_{21}H_{16}N_2O_5$=376).

Example 2

7-hydroxymethylcamptothecin (200 mg, 0.529 m-mol) was dissolved in acetic acid (100 ml) and the solution was boiled under reflux for 5.5 hours. Th reaction mixture was concentrated until dryness under reduced pressure and th residue was subjected to separation and purification by way of column chromatography ($CHCl_3$) on silica gel (30 g) whereby 7-acetoxymethylcamptothecin (19 mg, yield: 8.5%) and camptothecin-7-aldehyde (135 mg, yield: 67.8%) were obtained.

Example 3

7-Hydroxymethylcamptothecin (100 mg, 0.264 m-mol) was suspended in tetrachloroethane-dioxane (30 ml—20 ml). Boron trifluoride-ether (500 µl, about 3.96 m-mol) was added to the suspension and the whole was boiled under reflux for 14.5 hours. The reaction mixture was concentrated until dryness under reduced pressure and the residue was suspended in water (100 ml) and extracted with chloroform (100 ml × 3). The chloroform layers were combined, dried over magnesium sulfate, filtered and concentrated until dryness under reduced pressure. The residue was purified by way of column chromatography (chloroform) on silica gel whereupon 26 mg (yield: 26.1%) of camptothecin-7-aldehyde was obtained as yellow crystals.

Example 4

7-Hydroxycamptothecin (378 mg, 1 m-mol) was dissolved in pyridine (200 ml) while warm. p-Toluenesulfonyl chloride (950 mg, 5 m-mol) was added to the solution and the mixture was stirred for 4.5 hours at 80—90°C. The reaction mixture was concentrated until dryness under reduced pressure and the residue was subjected to separation and purification by way of column chromatography ($CHCl_3$) on silica gel whereby 255 mg (yield: 68.7%) of camptothecin-7-aldehyde was obtained as a yellow solid.

Example 5

7-Hydroxymethylcamptothecin (100 mg, 0.264 m-mol) was dissolved in pyridine (50 ml) and dimethylformamide (50 ml). Phenylacetyl chloride (200 mg, 1.29 m-mol) was added to the solution and the mixture was stirred for 6 hours at 90—100°C. The reaction mixture was concentrated until dryness under reduced pressure and the residue was subjected to separation and purification by way of column chromatography ($CHCl_3$) on silica gel whereby 7-phenylacetoxymethylcamptothecin (74 mg, yield: 56.5%) and camptothecin-7-aldehyde (19 mg, yield: 19.1%) were obtained.

Example 6

7-Hydroxymethylcamptothecin (100 mg, 0.268 m-mol) was suspended in dioxane-chloroform (15 ml—7 ml). Phosphorus oxychloride (0.5 ml, 5.37 m-mol) was added to the suspension and the mixture was boiled under reflux for 2 hours. The reaction mixture was concentrated until dryness under reduced pressure and the residue was subjected to separation and purification by way of column chromatography ($CHCl_3$) on silica gel whereby 34 mg (yield: 34.2%) of camptothecin-7-aldehyde was obtained as a yellow solid.

Example 7

7-Hydroxymethylcamptothecin (100 mg, 0.264 m-mol) was suspended in dioxane-chloroform (75 ml—25 ml). Thionyl chloride (680 mg, 5.71 m-mol) was added to the suspension and the mixture was boiled under reflux for 14 hours. The reaction mixture was concentrated until dryness under reduced pressure and the residue was purified by way of column chromatography (chloroform) on silica gel whereby 57 mg (yield: 57.2%) of camptothecin-7-aldehyde was obtained as a yellow solid.

Example 8

7-Hydroxymethylcamptothecin (200 mg, 0.529 m-mol) was dissolved in dimethylformamide (150 ml) while warm. Triphenylphosphine (700 mg, 2.67 m-mol) and carbon tetrachloride (300 µl, ca. 3.11 m-mol) were added to the solution and the mixture was stirred for 10 hours at 95—100°C. The reaction mixture was concentrated until dryness under reduced pressure and the residue was subjected to separation and purification whereby 101 mg (yield: 56.4%) of camptothecin-7-aldehyde was obtained as a yellow solid. A small amount (about 20 mg) of 7-hydroxymethylcamptothecin was recovered.

Example 9

7-Hydroxymethylcamptothecin (100 mg, 0.264 m-mol) was suspended in methanol-dioxane (20 ml—20 ml) and conc. sulfuric acid (3 ml) was added to the suspension to form a solution. The mixture was boiled under reflux for 35 hours and then concentrated until dryness under reduced pressure. The residue was leached with H_2O (100 ml) and then extracted with $CHCl_3$ (100 ml × 3). The $CHCl_3$ phase was dried with $MgSO_4$, filtered and concentrated until dryness under reduced pressure. The residue was subjected to separation and purification by way of column chromatography ($CHCl_3$) on silica gel whereby 7-dimethoxymethylcamptothecin (19 mg, yield: 17.0%) and 7-methoxymethylcamptoth cin (40 mg, yield: 38.6%) were obtained.

Analytical data of these products are as follows:

(1) 7-methoxymethylcamptothecin
light yellowish white needle crystals
M.P. 252—257° (dec.) (methan l-chloroform).
IR ν_{max}^{KBr} cm^{-1}: 3350, 2920, 1755, 1655, 1600, 1115, 760.
NMR (DMSO-d_6) δ: 0.94 (3H, t, J=7 Hz), 1.88 (2H, q, J=7 Hz), 3.31 (3H, s), 5.20 (2H, s), 5.36 (2H, s), 5.46 (2H, s), 6.51 (1H, s, D_2O exchangeable), 7.39 (1H, s), 7.60—8.30 (4H, m).
MS: m/e 392 [M^+] ($C_{22}H_{20}N_2O_6$=392).
(2) 7-dimethoxymethylcamptothecin
light yellowish white needle crystals
M.P. 222—224° (dec.) (n-hexane-chloroform).
IR ν_{max}^{KBr} cm^{-1}: 3340, 2950, 2920, 1750, 1655, 1440, 1155, 1050, 750.
NMR ($CDCl_3$) δ: 1.05 (3H, t, J=7 Hz), 1.90 (2H, q, J=7 Hz), 3.40 (3H, s), 3.41 (3H, s), 5.29 (1H, d, J=16 Hz), 5.49 (2H, s), 5.77 (1H, d, J=16 Hz), 6.25 (1H, s), 7.67 (1H, s), 7.67—8.34 (4H, m).
MS: m/e 422 [M^+] ($C_{23}H_{22}N_2O_6$=422).

Example 10

7-Hydroxymethylcamptothecin (200 ml, 0.529 m-mol) was suspended in ethanol (20 ml) and conc. sulfuric acid (6 ml) was added to the suspension to form a solution. The solution was boiled under reflux for 7 hours and the reaction mixture was concentrated until dryness under reduced pressure. The residue was leached with H_2O (500 ml) and extracted with chloroform (200 ml × 3). A solid insoluble to both of the aqueous phase and the chloroform phase was collected by filtration (recovery of 7-hydroxymethylcamptothecin). The chloroform layers were combined, dried over $MgSO_4$ and concentrated until dryness and the residue was purified by way of column chromatography ($CHCl_3$) on silica gel whereby 7-diethoxymethylcamptothecin (24 mg, yield: 16%) and 7-ethoxymethylcamptothecin (27 mg, yield: 20.7%) were obtained. A small amount of 7-hydroxymethylcamptothecin was also recovered (79 mg in total amounts recovered).

Analytical data:

(1) 7-ethoxymethylcamptothecin
Light yellowish white needle crystals
M.P. 139—142° (ethanol-chloroform).
IR ν_{max}^{KBr} cm^{-1}: 3400, 2950, 2920, 2860, 1745, 1655, 1600, 1230, 1155, 760.
NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.3 Hz), 1.38 (3H, t, J=6.8 Hz), 1.83 (2H, q, J=7.3 Hz), 3.81 (2H, q, J=6.8 Hz), 5.18 (2H, s), 5.27 (1H, d, J=16.6 Hz), 5.43 (2H, s), 5.76 (1H, d, J=16.6 Hz), 7.65 (1H, s), 7.65—8.28 (4H, m).
MS: m/e 406[M^+] ($C_{23}H_{22}N_2O_5$=406).
(2) 7-diethoxymethylcamptothecin.
Light yellowish white needle crystals.
M.P. 223—224° (dec.) (ethanol).
IR ν_{max}^{KBr} cm^{-1}: 3400, 2960, 2920, 2880, 1740, 1655, 1600, 1155, 1050, 765.
NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7.3 Hz), 1.26 (3H, t, J=6.8 Hz), 1.28 (3H, t, J=6.8 Hz), 1.90 (2H, q, J=7.3 Hz), 3.70 (4H, m), 5.29 (1H, d, J=16 Hz), 5.50 (2H, s), 5.76 (1H, d, J=16 Hz), 6.36 (1H, s), 7.66 (1H, s), 7.64—6.87 (2H, m), 8.19—8.39 (2H m).
MS: m/e 450 [M^+] ($C_{25}H_{26}N_2O_6$=450).

Example 11

Camptothecin-7-aldehyde (200 mg, 0.532 m-mol) was dissolved in ethanol (50 ml). Boron trifluoride-ether (1 ml) was added to the solution and the mixture was boiled under reflux for 3.5 hours. The reaction mixture was concentrated until dryness under reduced pressure and the residue was shaken with water (100 ml) and chloroform (100 ml). The aqueous phase was further extracted with chloroform (100 ml). The chloroform layers were combined, dried over magnesium sulfate, filtered and concentrated until dryness under reduced pressure. The residue was purified by way of column chromatography (10% n-hexane-chloroform) on silica gel whereby 209 mg (yield: 87.3%) of 7-diethoxymethylcamptothecin was obtained as yellowish white crystals.

Example 12

7-Hydroxymethylcamptothecin (50 mg, 0.132 m-mol) was suspended in n-butanol (40 ml). Concentrated sulfuric acid (2 drops) were added to the suspension and the mixture was boiled under reflux for 30 minutes. The reaction mixture was concentrated until dryness under reduced pressure and the residue was leached with water (100 ml) and extracted with chloroform (100 ml × 3). The chloroform layers were combined, dried over $MgSO_4$, filtered and concentrated until dryness under reduced pressure. The residue was purified by way of column chromatography ($CHCl_3$) on silica gel whereby 26 mg (yield: 38.7%) of 7-dibutoxymethylcamptothecin was obtained as light yellowish white crystals. Analytical data of this product were as shown below.

M.P. 107—111° (n-hexane-chloroform).
IR ν_{max}^{KBr} cm^{-1}: 3400, 2950, 2930, 2860, 1750, 1660, 1610, 1590, 1155, 1050, 765.
NMR ($CDCl_3$) δ: 0.88 (6H, t, J=7Hz), 1.11 (3H, t, J=7 Hz), 1.14—1.79 (8H, m), 1.90 (2H, q, J=7 Hz), 3.57

(4H, m), 5.29 (1H, d, J=16 Hz), 5.50 (2H, s), 5.77 (1H, d, J=16 Hz), 6.36 (1H, s), 7.68 (1H, s), 7.50—7.80 (2H, m), 8.20—8.40 (2H, m).

MS: m/e 506 [M$^+$] ($C_{29}H_{34}N_2O_6$=506).

Example 13

Camptothecin-7-aldehyde (350 mg, 0.93 m-mol) was dissolved in a mixture of ethanol (70 ml) and pyridine (10 ml) while warm. Hydroxylamine hydrochloride (200 mg, 2.88 m-mol) was added to the solution and the mixture was refluxed for 30 minutes. After allowing the mixture to stand for cooling, the precipitated crystals were collected by filtration and dried under reduced pressure whereby 315 mg (yield: 36.5%) of camptothecin-7-aldehyde oxime was obtained. By concentrating the filtrate until dryness, additional 17 mg (4.7%) of this product was obtained.

M.P. 255—257°C (dec.).

IR ν_{max}^{KBr} cm^{-1}: 3300, 2970, 1740, 1655, 1590, 1155, 1005, 763.

NMR (DMSO-d_6) δ ppm: 0.90 (3H, t, J=7.5 Hz), 1.92 (2H, 1, J=7.5 Hz), 5.34 (2H, s), 5.43 (2H, s), 7.63 (1H, s), 7.75—8.34 (4H, m), 9.26 (1H, s), 12.54 (1H, s).

MS: m/e 391 [M$^+$] ($C_{21}H_{17}N_3O_3$=391).

Example 14

Camptothecin-7-aldehyde (150 mg, 0.399 m-mol) was dissolved in a mixture of ethanol (40 ml) and pyridine (3 ml) while warm. 80% Hydrazine hydrate (100 mg, 1.6 m-mol) was added to this solution and the mixture was refluxed for 15 minutes. After allowing the mixture to stand for cooling, precipitated crystals were collected by filtration and dried under reduced pressure whereby 110 mg (71.0%) of camptothecin-7-aldehyde hydrazone was obtained. By concentrating the filtrate until dryness, additional 15 mg (9.7%) of this product was obtained.

M.P. 262—265°C (dec.).

IR ν_{max}^{KBr} cm^{-1}: 3400, 2980, 1755, 1655, 1590, 1160, 1045, 763.

Example 15

Camptothecin-7-aldehyde (50 mg, 0.133 m-mol) was dissolved in a mixture of ethanol (20 ml) and pyridine (1 ml) while warm. Methylhydrazine (100 mg, 2.17 m-mol) was added to the solution and the mixture was refluxed for 30 minutes. After concentrating the mixture until dryness under reduced pressure, the residue was washed with ethanol and the precipitated crystals were collected by filtration whereupon 40 mg (74.4%) of camptothecin-7-aldehyde methylhydrazine was obtained.

M.P. 203—205°C (dec.).

IR ν_{max}^{KBr} cm^{-1}: 3250, 2950, 1740, 1650, 1500, 1370, 1150, 1030, 760.

NMR ($CDCl_3$—DMSO-d_6) δ ppm: 0.95 (3H, t, J=7 Hz), 1.88 (2H, q, J=7 Hz), 3.13 (3H, d, J=4 Hz), 5.35 (2H, s), 5.40 (2H, dxd, J=14 Hz), 6.25 (1H, bs), 7.43 (1H, s), 7.5—8.8 (4H, m), 10.15 (1H, bs).

MS: m/e 404 [M$^+$].

Example 16

Camptothecin-7-aldehyde (40 mg, 0.106 m-mol) was dissolved in a mixture of ethanol (15 ml) and pyridine (1 ml) while warm. Phenylhydrazine hydrochloride (25 mg, 0.173 m-mol) and sodium acetate (15 mg, 0.208 m-mol) were added to the solution and the mixture was refluxed for 10 minutes. After allowing the mixture to stand for cooling, water (15 ml) was added thereto and the precipitated crystals were collected by filtration whereby 35 mg (70.9%) of camptothecin-7-aldehyde phenylhydrazone was obtained.

M.P. 205—208°C (dec.).

IR ν_{max}^{KBr} cm^{-1}: 3240, 1735, 1655, 1600, 1530, 1495, 1255, 1157, 750.

NMR ($CDCl_3$-DMSO-d_6) δ ppm: 0.97 (3H, t, J=7 Hz), 1.90 (2H, q, J=7Hz), 5.44 (2H, dxd, J=16 Hz), 5.48 (2H, s), 6.90 (1H, bs), 7.0—8.9 (9H, m), 7.48 (1H, s), 11.24 (1H, s).

MS: m/e 466 [M$^+$].

Example 17

Camptothecin-7-aldehyde (50 mg, 0.133 m-mol) was dissolved in a mixture of ethanol (15 ml) and pyridine (1 ml) while warm. Acetic acid (2 ml) and 2,4-dinitrophenylhydrazine (50 mg, 0.253 m-mol) were added to the solution and the mixture was refluxed for 30 minutes. After allowing the mixture to stand for cooling, the precipitated crystals were collected by filtration whereupon 60 mg (81.1%) of camptothecin-7-aldehyde 2,4-dinitrophenylhydrazone was obtained.

M.P. 262—264°C (dec.).

IR ν_{max}^{KBr} cm^{-1}: 3520, 3270, 2880, 1720, 1655, 1590, 1500, 1320, 1220, 1135, 825, 765.

NMR ($CDCl_3$-DMSO-d_6) δ ppm: 0.97 (3H, t, J=7 Hz), 1.89 (2H, q, J=7 Hz), 5.43 (2H, dxd, J=16 Hz), 5.47 (2H, s), 7.46 (1H, s), 7.6—8.9 (7H, m), 9.86 (1H, s), 12.13 (1H, s).

MS: m/e 556 [M$^+$].

Example 18

Camptothecin-7-aldehyde (100 ml, 0.27 m-mol) was dissolved in a mixture of ethanol (40 ml) and pyridine (3 ml) under warming. 1-Amino-4-methylpiperazine dihydrochloride mon hydrate (100 mg, 0.49 m-mol) was added to th solution and the mixture was refluxed for 30 minutes. After allowing the mixture to stand for cooling, the precipitated crystals were collected by filtration and dri d under reduced pr ssure whereupon 120 mg (82.6%) of camptothecin-7-aldehyde 4-methylpiperazinohydrazone hydrochloride was obtained.

M.P. 250°C (dec.).

IR ν_{max}^{KBr} cm^{-1}: 3400, 2950, 2650, 2580, 2450, 1743, 1655, 1600, 1545, 1370, 1155, 970, 763.

This hydrochloride was treated with a 15% aqueous solution of sodium carbonate and the precipitate was extracted with chloroform. The chloroform phase was dried over magnesium sulfate and concentrated until dryness whereby the free hydrazone was obtained quantitatively.

NMR ($CDCl_3$) δ ppm: 1.05 (3H, t, J=7 Hz), 1.89 (2H, q, J=7 Hz), 2.44 (3H, s), 2.72 (4H, t), 3.53 (4H, t), 5.41 (2H, s), 5.51 (2H, dxd, J=16 Hz), 7.62 (1H, s), 7.4—8.3 (5H, m).

MS: m/e 473 [M^+].

Example 19

Camptothecin-7-aldehyde (100 mg, 0.266 m-mol) was dissolved in a mixture of ethanol (40 ml) and pyridine (3 ml) while warm. Pyridinium acetohydrazide chloride (50 mg, 0.269 m-mol) was added to the solution and the mixture was refluxed for 30 minutes. After allowing the mixture to stand for cooling, the precipitated crystals were collected by filtration and dried under reduced pressure whereby 80 mg (55.1%) of a hydrazone of camptothecin-7-aldehyde with pyridinium acetohydrazide chloride was obtained.

M.P. 255°C (dec.).

IR ν_{max}^{KBr} cm^{-1}: 3440, 3050, 2950, 1740sh, 1700, 1655, 1595, 1155, 765.

Example 20

Camptothecin-7-aldehyde (30 mg, 0.080 m-mol) was dissolved in a mixture of ethanol (10 ml) and pyridine (1 ml) while warm. Thiosemicarbazide (27 mg, 0.296 m-mol) was added to the solution and the mixture was refluxed for 3 hours. After concentrating the mixture until dryness under reduced pressure, the residue was washed with ethanol and the precipitated crystals were collected by filtration and dried under reduced pressure whereby 28 mg (78.3%) of camptothecin-7-aldehyde thiosemicarbazone was obtained.

M.P. 263°C (dec.).

IR ν_{max}^{KBr} cm^{-1}: 3250, 3180, 2970, 1740, 1650, 1590, 1395, 1280, 1155, 830, 760.

NMR (DMSO-d_6) δ ppm: 0.89 (3H, t, J=7 Hz), 0.95 (2H, q, J=7 Hz), 5.43 (2H, s), 5.62 (2H, s), 7.37 (1H, s), 7.8—8.8 (6H, m), 9.10 (1H, s), 11.88 (1H, s).

Example 21

Camptothecin-7-aldehyde (40 mg, 0.106 m-mol) was dissolved in a mixture of ethanol (10 ml) and pyridine (1 ml) while warm. Semicarbazide hydrochloride (15 mg, 0.134 m-mol) was added to the solution and the mixture was refluxed for 30 minutes. After allowing the mixture to stand for cooling, the precipitated crystals were collected by filtration, washed with ethanol and dried under reduced pressure whereby 42 mg (91.2%) of camptothecin-7-aldehyde semicarbazone was obtained.

M.P. 280°C (dec.).

IR ν_{max}^{KBr} cm^{-1}: 3480, 3300, 1740, 1690, 1655, 1585, 1400, 1100, 760.

NMR (DMSO-d_6) δ ppm: 0.90 (3H, t, J=7 Hz), 1.88 (2H, q, J=7 Hz), 5.43 (2H, s), 5.53 (2H, s), 6.65 (2H, bs), 7.35 (1H, s), 7.8—8.3 (4H, m), 8.86 (1H, s), 10.85 (1H, s).

Example 22

Camptothecin-7-aldehyde (200 mg, 0.532 m-mol) was dissolved in ethanol (50 ml) and boron trifluoride-ether (1 ml) was then added to the solution. The mixture was boiled under reflux for 3.5 hours. The reaction mixture was concentrated until dryness under reduced pressure and the residue was shaken with water (100 ml) and chloroform (100 ml). The aqueous phase was extracted with additional chloroform (100 ml). The chloroform layers were combined, dried over magnesium sulfate, filtered and concentrated until dryness under reduced pressure. The residue was purified by way of column chromatography (10% n-hexanechloroform) on silica gel whereby 209 mg (yield: 87.3%) of 7-diethoxymethylcamptothecin was obtained as yellowish white crystals.

Analytical data of this compound were identical with those shown in Example 10.

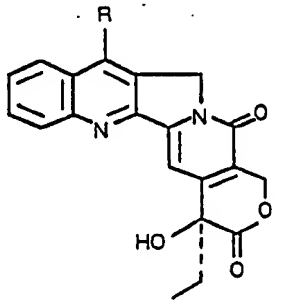
Example 23

7-Diethoxymethylcamptothecin (250 mg, 0.555 m-mol) was suspended in ice water (15 ml) and conc. hydrochloric acid (25 ml) was added thereto to form a solution. The mixture was stirred for 18 hours at room temperature, diluted with ice water (500 ml) and then extracted with chloroform (200 ml × 3). The chl roform layers were dried ver magnesium sulfate, filtered and concentrated until dryness under reduced pressur whereby 187 mg (yield: 89.6%) of camptothecin-7-ald hyde was obtain d as a yellow solid.

Analytical data of this product were identical with those shown in Example 1.

Claims

1. 7-substituted camptothecin derivatives of the general formula:



(I)

wherein R represents —CHO, —CH_2OR'', —$CH(OR')_2$, or —CH=N—X where R' is a lower alkyl group having from 1 to 6 carbon atoms or a phenylalkyl group having from 1 to 3 carbon atoms in the alkylene moiety thereof, R'' is a phenylalkyl group having from 1 to 3 carbon atoms in the alkylene moiety thereof, and X is a hydroxyl group or —NR^1R^2 where R^1 and R^2 are the same or different and each represent hydrogen atom or a lower alkyl group having from 1 to 6 carbon atoms, or when R^1 is hydrogen, R^2 may be a lower alkyl group having from 1 to 6 carbon atoms, a substituted or unsubstituted aryl group, a carbamoyl group, an acyl group, an aminoalkyl group or an amidino group, or when R^1 is a lower alkyl group, R^2 may be an aminoalkyl group, or R^1 and R^2 may be combined together with the nitrogen atom to which they are attached to form a heterocyclic group which may be interrupted by one or two nitrogen, oxygen and/or sulphur atoms, and the quaternary salts thereof.

2. 7-substituted camptothecin derivatives as claimed in Claim 1 wherein R represents the group —$CH(OR')_2$ where R' is a straight or branched chain alkyl group having from 1 to 6 carbon atoms.

3. 7-substituted camptothecin derivatives as claimed in Claim 1 wherein R represents the group —CH_2OR' where R' is a phenylalkyl group having from 1 to 3 carbon atoms in the alkylene moiety.

4. 7-substituted camptothecin derivatives as claimed in Claim 1 wherein R represents the group —$CH(OR')_2$ where R' is a phenylalkyl group having from 1 to 3 carbon atoms in the alkylene moiety which is linear or branched.

5. Camptothecin-7-aldehyde.

6. Camptothecin-7-aldehyde oxime.

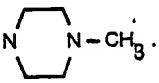
7. Camptothecin-7-aldehyde hydrazone.

8. 7-substituted camptothecin derivatives as claimed in Claim 1 wherein R represents the group —CH=N—X and X is the group —NR^1R^2 where R^1 is hydrogen and R^2 is a straight or branched chain alkyl group having from 1 to 6 carbon atoms.

9. 7-substituted camptothecin derivatives as claimed in Claim 1 wherein R represents the group —CH=N—X and X is the group —NR^1R^2 where R^1 is hydrogen and R^2 is an unsubstituted phenyl group or a phenyl group substituted by one or two nitro groups in the o- and/or p-positions thereof.

10. Camptothecin-7-aldehyde p-toluenesulfonylhydrazone.

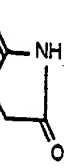
11. Camptothecin-7-CH = N–N = $C(NH_2)_2$.

12. Camptothecin-7-CH = N–  .

13. Camptothecin-7-CH = N–$NHCOCH_2N(CH_3)_2 \cdot HCl$

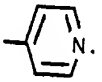
14. Camptothecin-7-CH = N–$NHCOCH_2N(CH_3)_3 \cdot Cl$

15. Camptothecin-7-CH = N–NHCOCH$_2$N⁺·Cl⁻



16. Camptothecin-7-CH = N–N

17. Camptothecin-7-CH = N–NHCO–



18. Camptothecin-7-aldehyde semicarbazone.

19. Camptothecin-7-aldehyde phenylsemicarbazone.

20. Camptothecin-7-aldehyde thiosemicarbazone.

21. Camptothecin-7-CH = N–N

22. A process for the preparation of camptothecin-7-aldehyde from 7-hydroxymethylcamptothecin, which comprises treating 7-hydroxymethylcamptothecin with a cationic reagent which is an inorganic acid, organic acid, a Lewis acid, an organic acid halide or a halogenating agent.

23. A process as claimed in Claim 22 wherein the inorganic acid is sulfuric acid, hydrochloric acid, hydrobromic acid, perchloric acid or hydroiodic acid.

24. A process as claimed in Claim 22 wherein the organic acid is acetic acid, propionic acid, benzoic acid, chloroacetic acid, trifluoroacetic acid, p-toluenesulfonic acid, methanesulfonic acid or ethanesulfonic acid.

25. A process as claimed in Claim 22 wherein the Lewis acid is boron trifluoride etherate, aluminium chloride, ferric chloride or stannic chloride.

26. A process as claimed in Claim 22 wherein the organic acid halide is p-toluenesulfonyl chloride or phenylacetyl chloride.

27. A process as claimed in Claim 22 wherein the halogenating agent is phosphorus oxychloride, phosphorus trichloride, thionyl chloride or triphenylphosphite-carbon tetrachloride.

28. A process as claimed in Claim 22 or Claim 23 wherein the inorganic acid is used as a 20—50% aqueous solution and the reaction is carried out under reflux.

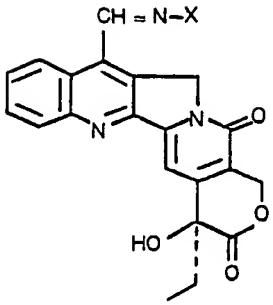
29. A process as claimed in Claim 22 or Claim 24 wherein the organic acid is used in a polar solvent.

30. A process as claimed in Claim 22 or Claim 25 wherein the Lewis acid is used in a 5 to 10 molar amount to the 7-hydroxymethylcamptothecin and the reaction is carried out at a temperature of 90—100°C in an aprotic solvent.

31. A process as claimed in Claim 22 or Claim 26 wherein the organic acid halide is used in a 5 to 10 molar amount to the 7-hydroxymethylcamptothecin and the reaction is carried at a temperature of 90 to 100°C in a polar solvent.

32. A process as claimed in Claim 22 or Claim 27 wherein the halogenating agent is used in a 5 to 10 molar amount to the 7-hydroxymethylcamptothecin and the reaction is carried out at a temperature of about 100°C in a solvent.

33. A process for the preparation of new 7-substituted camptothecin derivatives of the general formula:



(I'')

wherein X is a hydroxyl group or the group —NR^1R^2 where R^1 and R^2 are the same or different and each represent a hydrogen atom or a lower alkyl group having from 1 to 6 carbon atoms, or when R^1 is a hydrogen atom, R^2 may be a lower alkyl group having from 1 to 6 carbon atoms, a substituted or unsubstituted aryl group, a carbamoyl group, an acyl group, an aminoalkyl group or an amidino group, or when R^1 is a lower alkyl group, R^2 may be an aminoalkyl group, or R^1 and R^2 may be combined together with the nitrogen atom to which they are attached to form a heterocyclic group which may be interrupted by one or two nitrogen, oxygen and/or sulfur atoms, and the quaternary salts thereof, which process comprises reacting camptothecin-7-aldehyde or an acetal thereof with an active amino compound of the general formula:

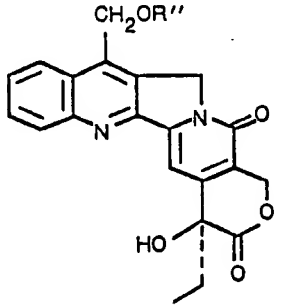
$$H_2N—X \qquad \text{(II)}$$

wherein X is as defined above, in a manner known per se and optionally treating the resultant product with a quaternizing agent.

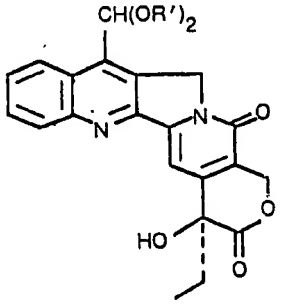
34. A process as claimed in Claim 33 wherein the active amino compound of the general formula (II) is hydroxylamine, hydrazine, a lower alkylhydrazine, phenyl hydrazine which may be ring-substituted with one or two nitro groups in the o- and/or p-positions, semicarbazide, Girard reagents, thiosemicarbazide or N-aminohydantoin.

35. A process as claimed in Claim 33 wherein the quaternizing agent is a lower alkyl halide or a strong acid.

36. A process for the preparation of 7-phenylalkoxymethyl- and 7-dialkoxymethylcamptothecin derivatives of the general formulae:



(I'''—A) and



(I'''—B)

wherein R' is a lower alkyl group having from 1 to 6 carbon atoms or a phenyl-alkyl group having from 1 to 3 carbon atoms in the alkylene moiety thereof and R'' is a phenyl-alkyl group having from 1 to 3 carbon atoms in the alkylene moiety thereof, which process comprises treating 7-hydroxymethylcamptothecin with an acid in the presence of a lower alkanol or phenylalkanol of the general formula:

$$R'—OH \text{ or } R''—OH \qquad \text{(III)}$$

wherein R' and R'' are as defined above.

37. A process as claimed in Claim 36 wherein the acid is a mineral acid, a Lewis acid, a strong organic carboxylic acid or an organic sulfonic acid.

38. A process as claimed in Claim 37 wherein the mineral acid is sulfuric acid, hydrochloric acid, hydrobromic acid or perchloric acid.

39. A process as claimed in Claim 37 wherein the Lewis acid is boron trifluoride, aluminium chloride, ferric chloride or stannic chloride.

40. A process as claimed in Claim 37 wherein the strong organic carboxylic acid is trifluoroacetic acid or trichloroacetic acid.

41. A process as claim d in Claim 37 wherein the organic sulfonic acid is benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid or ethanesulfonic acid.

42. A process as claimed in any one of Claims 36 to 41 wherein the lower alkanol is methanol, ethanol, propanol, isopropanol, n-butanol, tert-butanol, n-amyl alcohol, isoamyl alcohol, tert-amyl alcohol, n-hexanol or 2-ethylbutanol.

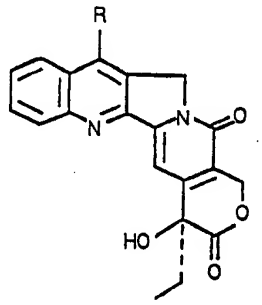
43. A process as claimed in any one of Claims 36 to 42 wherein the 7-hydroxymethylcamptothecin is maintained in the lower alkanol or phenylalkanol as solvent in the presence of the acid at a temperature from room temperature to reflux temperature.

44. A process as claimed in any one of Claims 36 to 43 wherein the acid is used in a catalytic amount or in an amount of several molar equivalents relative to the 7-hydroxymethylcamptothecin to obtain a 7-dialkoxymethylcamptothecin exclusively or preferentially.

45. A process as claimed in any one of Claims 36 to 43 wherein the acid is used in a large excess amount relative to the 7-hydroxymethylcamptothecin together with a phenylalkanol of the general formula R''—OH as defined in Claim 36 to obtain a 7-phenylalkoxymethylcamptothecin exclusively or preferentially.

Patentansprüche

1. 7-substituierte Camptothecin-Derivate der allgemeinen Formel



(I)

worin R = —CHO, —CH_2OR'', —$CH(OR')_2$ oder —CH = N—X darstellt, worin R' eine niedere Alkylgruppe mit 1 bis 6 Kohlenstoffatomen oder eine Phenylalkylgruppe mit 1 bis 3-Kohlenstoffatomen in der Alkylengruppe, R'' eine Phenylalkylgruppe mit 1 bis 3 Kohlenstoffatomen in der Alkylengruppe und X eine Hydroxylgruppe oder —NR^1R^2 bedeuten, worin R^1 und R^2 gleich oder voneinander verschieden sind und jeweils ein Wasserstoffatom oder eine niedere Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeuten oder, wenn R^1 Wasserstoff ist, R^2 eine niedere Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine substituierte oder unsubstituierte Arylgruppe, eine Carbamoylgruppe, eine Acylgruppe, eine Aminoalkylgruppe oder eine Amidogruppe sein kann, oder, wenn R^1 eine niedere Alkylgruppe ist, R^2 eine Aminoalkylgruppe sein kann, oder worin R^1 und R^2 mit dem Stickstoffatom, an das sie gebunden sind, unter Bildung einer heterocyclischen Gruppe kombiniert sein können, die durch ein oder zwei Stickstoff-, Sauerstoff- und/oder Schwefelatome unterbrochen sein kann; und deren quaternäre Salze.

2. 7-substituierte Camptothecin-Derivate nach Anspruch 1, worin R die Gruppe —$CH(OR')_2$ darstellt, worin R' eine gerade oder verzweigtkettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet.

3. 7-substituierte Camptothecin-Derivate nach Anspruch 1, worin R die Gruppe —CH_2OR' darstellt, worin R' eine Phenylalkylgruppe mit 1 bis 3 Kohlenstoffatomen in der Alkylengruppe bedeutet.

4. 7-substituierte Camptothecin-Derivate nach Anspruch 1, worin R die Gruppe —$CH(OR')_2$ darstellt, worin R' eine Phenylalkylgruppe mit 1 bis 3 Kohlenstoffatomen in der Alkylengruppe, die linear oder verzweigt ist, bedeutet.

5. Camptothecin-7-aldehyd.

6. Camptothecin-7-aldehyd-oxim.

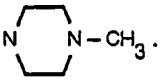
7. Camptothecin-7-aldehyd-hydrazon.

8. 7-substituierte Camptothecin-Derivate nach Anspruch 1, worin R die Gruppe —CH=N—X und X die Gruppe —NR^1R^2 darstellen, worin R^1 Wasserstoff und R^2 eine gerad- oder verzweigtkettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet.

9. 7-substituierte Camptothecin-Derivate nach Anspruch 1, worin R die Gruppe —CH=N—X und X die Gruppe —NR^1R^2 darstellen, worin R^1 Wasserstoff und R^2 eine unsubstituierte Phenylgruppe oder eine durch eine oder zwei Nitrogruppen in der o- und/oder p-Stellung substituierte Phenylgruppe bedeutet.

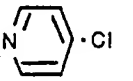
10. Camptothecin-7-aldehyd p-toluolsulfonylhydrozon.

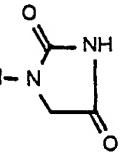
11. Camptothecin-7-CH = N–N = $C(NH_2)_2$.

12. Camptothecin-7-CH = N–  .

13. Camptothecin-7-CH = N–$NHCOCH_2N(CH_3)_2 \cdot HCl$

14. Camptothecin-7-CH = N–$NHCOCH_2N(CH_3)_3 \cdot Cl$

15. Camptothecin-7-CH = N–$NHCOCH_2N$  $\cdot Cl$

16. Camptothecin-7-CH = N– 

17. Camptothecin-7-CH = N–NHCO–  .

18. Camptothecin-7-aldehyd-semicarbazon.

19. Camptothecin-7-aldehyd-phenylsemicarbazon.

20. Camptothecin-7-aldehyd-thiosemicarbazon.

21. Camptothecin-7-CH = N–  .

22. Verfahren zur Herstellung von Camptothecin-7-aldehyd aus 7-Hydroxymethylcamptothecin, wobei 7-Hydroxymethylcamptothecin mit einem kationischen Reagens behandelt wird, welches eine anorganische Säure, eine organische Säure, eine Lewis-Säure, ein organisches Säurehalogenid oder ein Halogenierungsmittel darstellt.

23. Verfahren nach Anspruch 22, worin die anorganische Säure Schwefelsäure, Chlorwasserstoffsäure, Bromwasserstoffsäure, Perchlorsäure oder Jodwasserstoffsäure darstellt.

24. Verfahren nach Anspruch 22, worin die organische Säure Essigsäure, Propionsäure, Benzoesäure, Chloressigsäure, Trifluoressigsäure, p-Toluolsulfosäure, Methansulfonsäure oder Ethansulfonsäure darstellt.

25. Verfahren nach Anspruch 22, worin die Lewis-Säure Bortrifluorid-Etherat, Aluminiumchlorid, Ferrichlorid oder Stanichlorid darstellt.

26. Verfahren nach Anspruch 22, worin das organische Säurehalogenid p-Toluolsulfonylchlorid oder Phenylacetylchlorid darstellt.

27. Verfahren nach Anspruch 22, worin das Halogenierungsmittel Phosphoroxychlorid, Phosphortrichlorid, Thionylchlorid oder Triphenylphosphit-Tetrachlorkohlenstoff darstellt.

28. Verfahren nach Anspruch 22 oder 23, worin die anorganische Säure als 20—50%ige wäßrige Lösung verwendet und die Umsetzung unter Rückfluß durchgeführt wird.

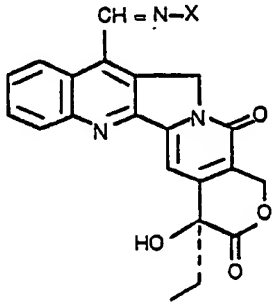
29. Verfahren nach Anspruch 22 oder 24, worin die organische Säure als polares Lösungsmittel verwendet wird.

30. Verfahren nach Anspruch 22 oder 25, worin die Lewis-Säure in einer 5- bis 10-molaren Menge, bezogen auf das 7-Hydroxymethylcamptothecin, verwendet, und die Umsetzung bei einer Temperatur von 90 bis 100°C in einem protonenfreien Lösungsmittel durchgeführt wird.

31. Verfahren nach Anspruch 22 oder 26, worin das organische Säurehalogenid in einer 5- bis 10-molaren Menge, bezogen auf das 7-Hydroxymethylcamptothecin, verwendet und die Umsetzung bei einer Temperatur von 90 bis 100°C in einem polaren Lösungsmittel durchgeführt wird.

32. Verfahren nach Anspruch 22 oder 27, worin das Halogenierungsmittel in einer 5- bis 10-molaren Menge, bezogen auf das 7-Hydr xymethylcamptothecin, verwendet und di Umsetzung bei einer Temperatur von etwa 100°C in einem Lösungsmittel durchgeführt wird.

33. Verfahren zur Herstellung v n neuen 7-substituierten Camptothecin-Derivaten der allgemeinen Formel



(I'')

worin X eine Hydroxylgruppe oder die Gruppe —NR^1R^2 darstellt, worin R^1 und R^2 gleich oder voneinander verschieden sind und jeweils ein Wasserstoffatom oder eine niedere Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeuten, oder, wenn R^1 ein Wasserstoffatom ist, R^2 eine niedere Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, eine substituierte oder unsubstituierte Arylgruppe, eine Carbamoylgruppe, eine Acylgruppe, eine Aminoalkylgruppe oder eine Amidinogruppe sein kann, oder, wenn R^1 eine niedere Alkylgruppe ist, R^2 eine Aminoalkylgruppe sein kann oder R^1 und R^2 zusammen mit dem Stickstoffatom, an das sie gebunden sind, unter Bildung einer heterocyclischen Gruppe miteinander kombiniert sein können, die durch ein oder zwei Stickstoff-Sauerstoff- und/oder Schwefelatome unterbrochen sein kann; und deren quanternären Salzen, dadurch gekennzeichnet, daß man Camptothecin-7-aldehyd oder ein Acetal davon mit einer aktiven Aminoverbindung der allgemeinen Formel

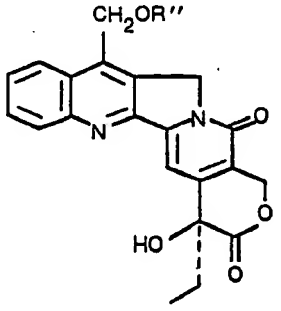
$$H_2N—X \qquad (II)$$

worin X wie vorstehend definiert ist, in an sich bekannter Weise umsetzt und das erhaltene Produkt gegebenenfalls mit einem Quaternisierungsmittel behandelt.

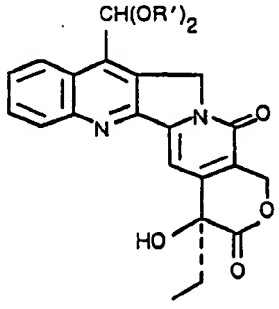
34. Verfahren nach Anspruch 33, worin die aktive Aminoverbindung der allgemeinen Formel (II) Hydroxylamin, Hydrazin, ein niederes Alkylhydrazin, Phenylhydrazin (das mit einer oder zwei Nitrogruppen in der o- und/oder p-Stellung ringsubstituiert sein kann), Semicarbazid, Girard-Reagentien, Thiosemicarbazid oder N-Aminohydantoin darstellt.

35. Verfahren nach Anspruch 33, worin das Quaternisierungsmittel ein niederes Alkylhalogenid oder eine starke Säure darstellt.

36. Verfahren zur Herstellung von 7-Phenylalkoxymethyl- und 7-Dialkoxymethylcamptothecin-Derivaten der allgemeinen Formeln



(I'''—A) und



(I'''—B)

worin R' eine niedere Alkylgruppe mit 1 bis 6 Kohlenstoffatomen oder eine Phenyl-Alkylgruppe mit 1 bis 3 Kohlenstoffatomen in der Alkylengruppe und R'' eine Phenyl-Alkylgruppe mit 1 bis 3 Kohlenstoffatomen in der Alkylengruppe darstellt, dadurch gekennzeichnet, daß man 7-Hydroxymethylcamptothecin- mit einer Säure in Gegenwart eines niederen Alkanols oder Phenylalkanols der allgemeinen Formel

$$R'—OH \text{ oder } R''—OH \qquad (III)$$

umsetzt, worin R' und R'' wie vorstehend definiert sind.

37. Verfahren nach Anspruch 36, w rin die Säure eine Mineralsäure, eine Lewis-Säure, eine starke organische Carbonsäure oder eine organische Sulfonsäure darstellt.

38. Verfahren nach Anspruch 37, worin die Mineralsäure Schwefelsäure, Schwefelsäure, Chlorwasserstoffsäure, Bromwasserstoffsäure oder Perchlorsäure darstellt.

39. Verfahren nach Anspruch 37, worin die Lewis-Säure Bortrifluorid, Aluminiumchlorid, Ferrichlorid oder Stannichlorid darstellt.

40. Verfahren nach Anspruch 37, worin die starke organische Carbonsäure Trifluoressigsäure oder Trichloressigsäure darstellt.

41. Verfahren nach Anspruch 37, worin die organische Sulfonsäure Benzolsulfonsäure, p-Toluolsulfonsäure, Methansulfonsäure oder Ethansulfonsäure darstellt.

42. Verfahren nach einem der Ansprüche 36 bis 41, worin der niedere Alkanol Methanol, Ethanol, Propanol, Isopropanol, n-Butanol, tert.-Butanol, n-Amylalkohol, Isoamylalkohol, tert.-Amylalkohol, n-Hexanol oder 2-Ethylbutanol darstellt.

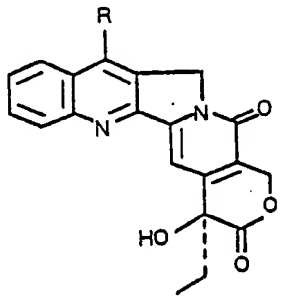
43. Verfahren nach einem der Ansprüche 36 bis 42, worin das 7-Hydroxymethylcamptothecin in dem neideren Alkanol oder Phenylalkohol als Lösungs-mittel in Gegenwart der Säure bei einer Temperatur von Raumtemperatur bis Rückflußtemperatur gehalten wird.

44. Verfahren nach einem der Ansprüche 36 bis 43, worin die Säure in einer katalytischen Menge oder in einer Menge von mehreren molaren Äquivalenten, bezogen auf das 7-Hydroxymethylcamptothecin verwendet wird, um ausschließlich oder bevorzugt 7-Dialkoxymethylcamptothecin zu erhalten.

45. Verfahren nach einem der Ansprüche 36 bis 43, worin die Säure in einem großen Überschuß, bezogen auf das 7-Hydroxymethylcamptothecin, zusammen mit einem Phenylalkanol der allgemeinen Formel R''—OH (wie in Anspruch 36 definiert) verwendet wird, um ausschließlich oder bevorzugt ein 7-Phenylakloxymethylcamptothecin zu erhalten.

Revendications

1. Dérivés substitués en 7 de la camptothécine ayant la formule généale:



(I)

dans laquelle R représente —CHO—, —CH_2OR'', —$CH(OR')_2$ ou —CH=N—X, où R' est un groupe alkyle inférieur ayant de 1 à 6 atomes de carbone ou un groupe phénylalkyle ayant de 1 à 3 atomes de carbone dans son radical alkylène; R'' est un groupe phénylalkyle ayant de 1 à 3 atomes de carbone dans son radical alkylène, et X est un groupe hydroxyle ou bien —NR^1R^2 où R^1 et R^2 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe alkyle inférieur ayant de 1 à 6 atomes de carbone, ou bien quand R^1 est un atome d'hydrogène, R^2 peut être un groupe alkyle inférieur ayant de 1 à 6 atomes de carbone, un groupe aryle substitué ou non substitué, un groupe carbamoyle, un groupe acyle, un groupe aminoalkyle ou un groupe amidino, ou bien quand R^1 est un groupe alkyle inférieur, R^2 peut être un groupe aminoalkyle, ou bien R^1 et R^2 peuvent être combinés ensemble avec l'atome d'azote auquel ils sont liés pour former un groupe hétérocyclique qui peut être interrompu par un ou deux atome(s) d'azote, d'oxygène et/ou de soufre, et les sels quaternaires de ces dérivés.

2. Dérivés substitués en 7 de la camptothécine tels que revendiqués dans la revendication 1, dans lesquels R représente le groupe —$CH(OR')_2$ où R' est un groupe alkyle à chaîne linéaire ou ramifiée ayant de 1 à 6 atomes de carbone.

3. Dérivés substitués en 7 de la camptothécine tels que revendiqués dans la revendication 1, dans lesquels R représente le groupe —CH_2OR' où R' est un groupe phénylalkyle ayant de 1 à 3 atomes de carbone dans le radical alkylène.

4. Dérivés substitués en 7 de la camptothécine tels que revendiqués dans la revendication 1, dans lesquels R représente le groupe —$CH(OR')_2$ où R' est un groupe phénylalkyle ayant de 1 à 3 atomes de carbone dans le radical alkylène qui est linéaire ou ramifié.

5. Camptothécine-7-aldéhyde.

6. Camptothécine-7-aldoxime.

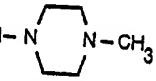
7. Camptothécine-7-aldéhyde hydrazone.

8. Dérivés substitués en 7 de la camptothécine tels que revendiqués dans la revendication 1, dans lesquels R représente le groupe —CH=N—X, et X est le groupe —NR^1R^2 où R^1 est un atome d'hydrogène, et R^2 est un groupe alkyle à chaîne linéaire ou ramifiée ayant de 1 à 6 atomes de carbone.

9. Dérivés substitués en 7 de la camptothécine tels que revendiqués dans la revendication 1, dans lesquels R représente le groupe —CH=N—X, et X est le groupe —NR^1R^2 où R^1 est un atome d'hydrogène, et R^2 est un groupe phényle non substitué ou bien un groupe phényle substitué par un ou deux groupe(s) nitro sur ses positions o- et/ou para.

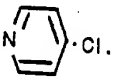
10. Camptothécine-7-aldéhyde p-toluènesulfonylhydrazone.

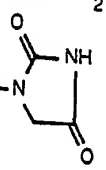
11. Camptothécine-7-CH = N—N = $C(NH_2)_2$.

12. Camptothécine-7-CH = N—  .

13. Camptothécine-7-CH = N—$NHCOCH_2N(CH_3)_2 \cdot HCl$.

14. Camptothécine-7-CH = N—$NHCOCH_2N(CH_3)_3 \cdot Cl$.

15. Camptothécine-7-CH = N—$NHCOCH_2$  .

16. Camptothécine-7-CH = N— 

17. Camptothécine-7-CH = N—NHCO—  .

18. Camptothécine-7-aldéhyde semicarbazone.

19. Camptothécine-7-aldéhyde-phénylsemicarbazone.

20. Camptothécine-7-aldéhyde-thiosemicarbazone.

21. Camptothécine-7-CH = N—  .

22. Procédé pour la préparation du camptothécine-7-aldéhyde à partir de la 7-hydroxyméthyl-camptothécine, qui consiste à traiter la 7-hydroxyméthylcamptothécine avec un réactif cationique qui est un acide minéral, un acide organique, un acide de Lewis, un halogénure d'acide organique ou un agent d'halogénation.

23. Procédé tel que revendiqué dans la revendication 22, dans lequel l'acide minéral est l'acide sulfurique, l'acide chlorhyridrique, l'acide bromhydrique, l'acide perchlorique ou l'acide iodhydrique.

24. Procédé tel que revendiqué dans la revendication 22, dans lequel l'acide organique est l'acide acétique, l'acide propionique, l'acide benzoïque, l'acide chloroacétique, l'acide trifluoroacétique, l'acide p-toluènesulfonique, l'acide méthanesulfonique ou l'acide éthanesulfonique.

25. Procédé tel que revendiqué dans la revendication 22, dans lequel l'acide de Lewis est l'éthérate de trifluorure de bore, le chlorure d'aluminium, le chlorure ferrique ou le chlorure stannique.

26. Procédé tel que revendiqué dans la revendication 22, dans lequel l'halogénure d'acide organique est le chlorure de p-toluènesulfonyle ou le chlorure de phénylacétyle.

27. Procédé tel que revendiqué dans la revendication 22, dans lequel l'agent d'halogénation est l'oxychlorure de phosphore, le trichlorure de phosphore, le chlorure de thionyl ou le triphénylphosphite-tétrachlorure de carbone.

28. Procédé tel que revendiqué dans la revendication 22 ou la revendication 23, dans lequel l'acide

minéral est utilisé sous forme d'une solution aqueuse à 20—50% et la réaction est effectué au reflux.

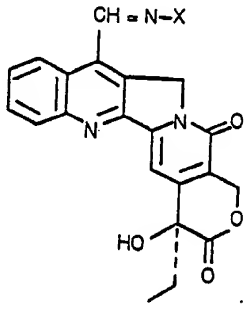
29. Procédé tel que revendiqué dans la revendicati n 22 ou la r vendication 24, dans lequel l'acide organique est utilisé dans un solvant polaire.

30. Procédé tel que revendiqué dans la revendication 22 ou la revendication 25, dans lequel l'acide de Lewis est utilisé en une quantité de 5 à 10 moles par rapport à la 7-hydroxyméthylcamptothécine et la réaction est effectuée à une température de 90—100°C dans un solvant aprotique.

31. Procédé tel que revendiqué dans la revendication 22 ou la revendication 26, dans lequel l'halogénure d'acide organique est utilisé en une quantité de 5 à 10 moles par rapport à la 7-hydroxyméthylcamptothécine et la réaction est effectuée à une température de 90 à 100°C dans un solvant polaire.

32. Procédé tel que revendiqué dans la revendication 22 ou la revendication 27, dans lequel l'agent d'halogénation est utilisé en une quantité de 5 à 10 moles par rapport à la 7-hydroxyméthylcamptothécine et la réaction est effectuée à une température d'environ 100°C dans un solvant.

33. Procédé pour la préparation de nouveaux dérivés substitués en 7 de la camptothécine ayant la formule générale:



(I'')

dans laquelle X est un groupe hydroxyle ou le groupe —NR^1R^2 où R^1 et R^2 sont identiques ou différents et représentent chacun un atome d'hydrogène ou un groupe alkyle inférieur ayant de 1 à 6 atomes de carbone, ou bien quand R^1 est un atome d'hydrogène, R^2 peut être une groupe alkyle inférieur ayant de 1 à 6 atomes de carbone, un groupe aryle substitué ou non substitué, un groupe carbamoyle, un groupe acyle, un groupe aminoalkyle ou un groupe amidino, ou quand R^1 est un groupe alkyle inférieur, R^2 peut être un groupe aminoalkyle ou bien R^1 et R^2 peuvent être combinés ensemble avec l'atome d'azote auquel ils sont liés pour former un groupe hétérocyclique qui peut être interrompu par un ou deux atome(s) d'azote, d'oxygène et/ou de soufre, et les sels quaternaires de ces dérivés, ces procédés, consistant à faire réagir la camptothécine-7-aldéhyde ou un acétal de celui-ci avec un composé amino actif ayant la formule générale:

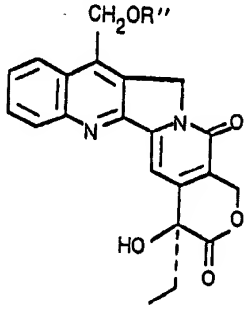
$$H_2N—X \qquad \text{(II)}$$

dans laquelle X a la définition ci-dessus, d'une façon connue en soi et à traiter éventuellement le produit résultant avec un agent de quaternisation.

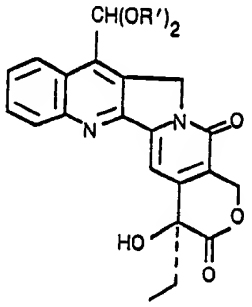
34. Procédé tel que revendiqué dans la revendication 33, dans lequel le composé amino actif de formule générale (II) est l'hydroxylamine, l'hydrazine, une alkylhydrazine inférieure, la phénylhydrazine qui peut être substituée sur le noyau par un ou deux groupes nitro sur les positions o- et/ou para, la semi-carbazide, les réactifs de Girard, la thiosemicarbazide ou la N-amino-hydantoïne.

35. Procédé tel que revendiqué dans la revendication 33, dans lequel l'agent de quaternisation est un halogénure d'alkyle inférieur ou un acide fort.

36. Procédé pour la préparation des dérivés 7-phénylalcoxyméthyl- et 7-dialcoxyméthylcamptothécine ayant les formules générales:



(I'''—A) et



(I'''—B)

dans lesquelles R' est un groupe alkyle inférieur ayant de 1 à 6 at mes d carbone ou un groupe phénylalkyle ayant de 1 à 3 atomes de carbone dans son radical alkylène, et R'' est un groupe phénylalkyle ayant de 1 à 3 atomes de carbone dans son radical alkylène, procédé qui consiste à traiter la 7-hydroxyméthylcamptothécine avec un acide en présence d'un alcanol inférieur ou d'un phénylalcanol ayant la formule générale:

$$R'—OH \text{ ou } R''—OH \qquad (III)$$

dans laquelle R' et R'' ont les définitions ci-dessus.

37. Procédé tel que revendiqué dans la revendication 36, dans lequel l'acide est un acide minéral, un acide de Lewis, un acide carboxylique organique fort ou un acide sulfonique organique.

38. Procédé tel que revendiqué dans la revendication 37, dans lequel l'acide minéral est l'acide sulfurique, l'acide chlorhydrique, l'acide bromhydrique ou l'acide perchlorique.

39. Procédé tel que revendiqué dans la revendication 37, dans lequel l'acide de Lewis est le trifluorure de bore, le chlorure d'aluminium, le chlorure ferrique ou le chlorure stannique.

40. Procédé tel que revendiqué dans la revendication 37, dans lequel l'acide carboxylique organique fort est l'acide trifluoroacétique ou l'acide trichloracétique.

41. Procédé tel que revendiqué dans la revendication 37, dans lequel l'acide sulfonique organique est l'acide benzènesulfonique, l'acide p-toluènesulfonique, l'acide méthanesulfonique ou l'acide éthanesulfonique.

42. Procédé tel que revendiqué dans l'une quelconque des revendications 36 à 41, dans lequel l'alcanol inférieur est le méthanol, éthanol, propanol, isopropanol, n-butanol, tert-butanol, alcool n-amylique, alcool isoamylique, alcool tert-amylique, le n-hexanol, ou le 2-éthylbutanol.

43. Procédé tel que revendiqué dans l'une quelconque des revendications 36 à 42, dans lequel la 7-hydroxyméthylcamptothécine est maintenue dans l'alcanol inférieur ou le phénylalcanol comme solvant en présence de l'acide à une température allant de la température ambiante à la température du reflux.

44. Procédé tel que revendiqué dans l'une quelconque des revendications 36 à 43, dans lequel l'acide est utilisé en une quantité catalytique ou en une quantité de plusieurs équivalents molaires par rapport à la 7-hydroxyméthylcamptothécine pour obtenir une 7-dialcoxyméthylcamptothécine exclusivement ou préférentiellement.

45. Procédé tel que revendiqué dans l'une quelconque des revendications 36 à 43, dans lequel l'acide est utilisé en un large excès par rapport à la 7-hydroxyméthylcamptothécine simultanément avec un phénylalcanol ayant la formule générale R''—OH tel que défini dans la revendication 36 pour obtenir une 7-phénylalcoxyméthylcamptothécine exclusivement ou préférentiellement.